JCHR (2022) 12(1), 7-13

Journal of Chemical Health Risks

www.jchr.org

ORIGINAL ARTICLE

Formaldehyde Carcinogenicity Risk Assessment Using Benchmark Doses Approach Based on Genotoxic Effects in Occupational Exposure

Rezvan Zendehdel[1], Masoomeh Vahabi[*2]

[1]*Department of Occupational Health and Safety, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[2]*Department of Occupational Health and Safety, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

Received: 21 April 2021 *Accepted: 7 September 2021)*

KEYWORDS

Benchmark dose;
Formaldehyde;
DNA damage;
Occupational exposure;
BMDL

ABSTRACT: Formaldehyde as a mass-produced chemical is used in many contexts. The genotoxicity and mutagenicity of formaldehyde are observed in different human body organs, such as buccal and white blood cells. The purpose of this study is to evaluate the lower confidence interval of benchmark dose (BMDL) for genotoxic damage of formaldehyde in the workplace, according to published studies. Studies from occupational genotoxic damage of formaldehyde were retrieved using search in databases such as Google Scholar, Web of Science, and PubMed until April 2020. The search strategy was established based on the words “formaldehyde”, “genotoxicity”, “carcinogenicity”, “DNA damage,” and “occupational exposure”. Based on dose-response data from three studies, benchmark dose (BMD) analysis was performed using EPA-BMD Software. Finally, five studies were included in the final BMDL conclusion. Polynomial and Hill models were used for BMDL evaluation in three studies, and BMD of formaldehyde was estimated between 0.062 to 0.26 ppm. The lowest level of BMDL (0.028 ppm) in five studies was considered the basic value for genotoxicity risk assessment. The estimated BMDL is approximated to the time-weighted average of the National Institute for Occupational Safety and Health (NIOSH). This value is suggested for the evaluation of the carcinogenic properties of formaldehyde.

INTRODUCTION

Formaldehyde, a toxic chemical, is utilized extensively in different industries [1]. As the mass-produced chemical, formaldehyde is used in resins such as phenolic, urea, and melamine and is also applied as a disinfectant and preservative for many applications [2]. In addition, during the metabolic reaction, trace amounts of formaldehyde are generated in the human body endogenously [3]. Inhalation exposure to formaldehyde commonly occurred in industries [4]. This chemical irritates the eye, nose, throat, and respiratory systems [5]. Inhalation of formaldehyde is related to carcinogenicity and the adverse toxic effects in the upper respiratory system [6-8]. In recent years, the carcinogenicity of formaldehyde has been confirmed in the pharyngeal, lymphohematopoietic, and nasal tissue [8-10].

Genotoxic effects of formaldehyde have been observed in various cells of humans and rodents [11]. DNA damage occurs in the bone marrow cell and peripheral blood lymphocytes of mice due to inhaled exposure to 0.41-2.44 ppm of formaldehyde [12]. Formaldehyde can also cause micronucleus and sister chromatid exchange in cells [11]. The Micronucleus effect of nasal mucosa

---

*Corresponding author: vahabimasume@yahoo.com; vahabimasume@sbmu.ac.ir (M. Vahabi)
DOI: 10.22034/jchr.2021.1928582.1296

cells among laboratory staff has been observed because prolonged exposure to 0.16 ppm of formaldehyde[13]. Moreover, micronucleus formation has been known in peripheral blood lymphocytes of workers exposed to formaldehyde[14].

Risk assessment is the process of determining harmful effects in people exposed to chemicals. One purpose of risk assessment is the creation of acceptable exposure levels for humans [15]. Traditionally, no observable adverse effect level (NOAEL) was utilized for health risk assessment [16]. Due to NOAEL limitations, BMD is used as an alternative for the NOAEL [17]. This approach has been advised by several agencies [18, 19].

The BMD was estimated for cytotoxicity effect in the rat [20] and irritation effect in human formaldehyde exposure [6]. In an experimental study, we evaluated a BMD level of DNA damage for occupationally exposed subjects in Iran[21]. This study aims to estimate BMD for different genotoxic effects in workers based on the published studies.

MATERIALS AND METHODS

Search strategyTo achieve the study's aims, reports and findings regarding the genotoxic effect of occupational exposure to formaldehyde were searched and retrieved. So, the keywords including “formaldehyde”, “genotoxicity”, “carcinogenicity”, “DNA damage”, “occupational exposure” and a combination of them was used. Search engines and databases of Google Scholar, Web of Science, and PubMed were systematically searched until April 2020. references of relevant studies were reviewed to achieve related papers missing in the search strategy. Only publications that studied genetic damage due to occupational exposure to formaldehyde were included.

Moreover, the studies that did not report the mean and standard deviation of formaldehyde concentrations and DNA damage were excluded. Based on inclusion and exclusion criteria, five eligible reports were selected for consideration. In the four studies, it was found that genetic damage was evaluated in blood cells, and in the remaining research, it was evaluated nasal mucosa. However, in tow studies [21, 22] were reported the BMDL level of formaldehyde in occupational exposure. The BMD and BMDL level of remaining three studies was estimated in this study. The specification of the selected papers was presented in Table 1.

Table 1. Characterization of selected studies

Country	Evaluated cells- Genotoxic test	Subject	Industry	Formaldehyde exposure-ppm (min-max)	Mean of work experience (year)
Italy [23]	Nasal mucosa- Micronucleus	15	Plywood	0.073-0.32	6
China [24]	Peripheral blood lymphocytes Micronucleus	151	Plywood	0.08-6.3	2.5
China [25]	Peripheral blood lymphocytes- Comet assay	178	Plywood	0.073-1.2	2.5
Iran [21]	Peripheral blood lymphocytes-Comet assay	53	Melamine dish producing	0.032-0.14	5.2
China [22]	Peripheral blood lymphocytes-Micronucleus	100	Chemical factory	0.008-0.4	9

BMD evaluation

BMD estimation was performed according to the United States Environmental Protection Agency-US EPA′s BMD software [16], version 3.1.2. The response of 1SD from control was applied for BMD estimation according to the continuous model. The mathematical functions of Exponential, Hill, Polynomial, Power, and Linear were used to estimate BMD and a 95% statistical confidence level lower BMD (BMDL). Based on the BMD software guideline, the suitable model was selected using criteria of goodness of p-value, $\chi 2$-scaled residual values, Akaike Information Criterion (AIC), and ocular inspection. The $\chi 2$-scaled residual value is used to evaluate local fit. As this value is closer to zero, it would indicate a better local fit among the doses. The US EPA recommended p-value ≥ 0.1, $\chi 2$-scaled residual values closer to zero, and lower AIC for better fitting. According to the BMD software guideline, higher BMDL was excluded from our deduction.

Genotoxic effects of formaldehyde

The genotoxic effects of formaldehyde were observed in chronic occupational exposures in the nasal mucosa cells by the Micronucleus method. Workers exposed to formaldehyde had a higher number of micronucleus in cells compared to the control group [23].

the occurrence of genetic damage examined using comet assay and micronucleus test in peripheral blood lymphocytes in workers exposed to formaldehyde. The exposure group showed higher levels of olive TM and micronucleus compared to the control group. Age, smoking status, and alcohol had no significant impact on any of the two biomarkers [24]

It was observed that exposure to formaldehyde led to DNA string break in peripheral blood lymphocytes of workers. The DNA string break was measured using the Comet test and oliv tail movement parameter [25].

RESULTS

The risk of genotoxicity was evaluated by BMD and BMDL levels in the published papers (Table 2). We counted BMDL between 0.03 to 0.18 ppm and BMD between 0.062 to 0.26 ppm from studies [23-25]. Also [21, 22] were evaluated BMDL 0.028 and 0.034 ppm for occupational exposure in previous studies.

Table 2. BMDL level of formaldehyde in occupational exposure.

Reference	Effect	BMD (ppm)	BMDL (ppm)
[23]	chromosome damage	0.062	0.03
[24]	chromosome damage	0.09	0.04
[25]	DNA strand breaks	0.26	0.18
[21]	DNA strand breaks	0.08	0.028
[22]	chromosome damage	0.054	0.034

In our modeling, different models in studied publications fitted the effect of formaldehyde exposure. Polynomial, Hill, and polynomial degree 2 were optimized for BMDL calculation. In Table 3, the specification of optimum models for BMD evaluation is presented.

Table 3. Characterize of optimum models.

Reference	Effect	Selected model	P-value Test	AIC	Scaled residual
[23]	chromosome damage	Polynomial	0.32	7.15	0.14
[24]	chromosome damage	Hill	0.36	1151.5	-0.56
[25]	DNA strand breaks	Polynomial degree 2	0.42	297.3	-0.33

Dose-response curve was plotted for each study to highlighted data fitting for each study (Figure 1). The genotoxicity effect in different formaldehyde exposure was plotted according to mathematical functions. The dose-response curve for the fitted models in each study was presented in Figure1.

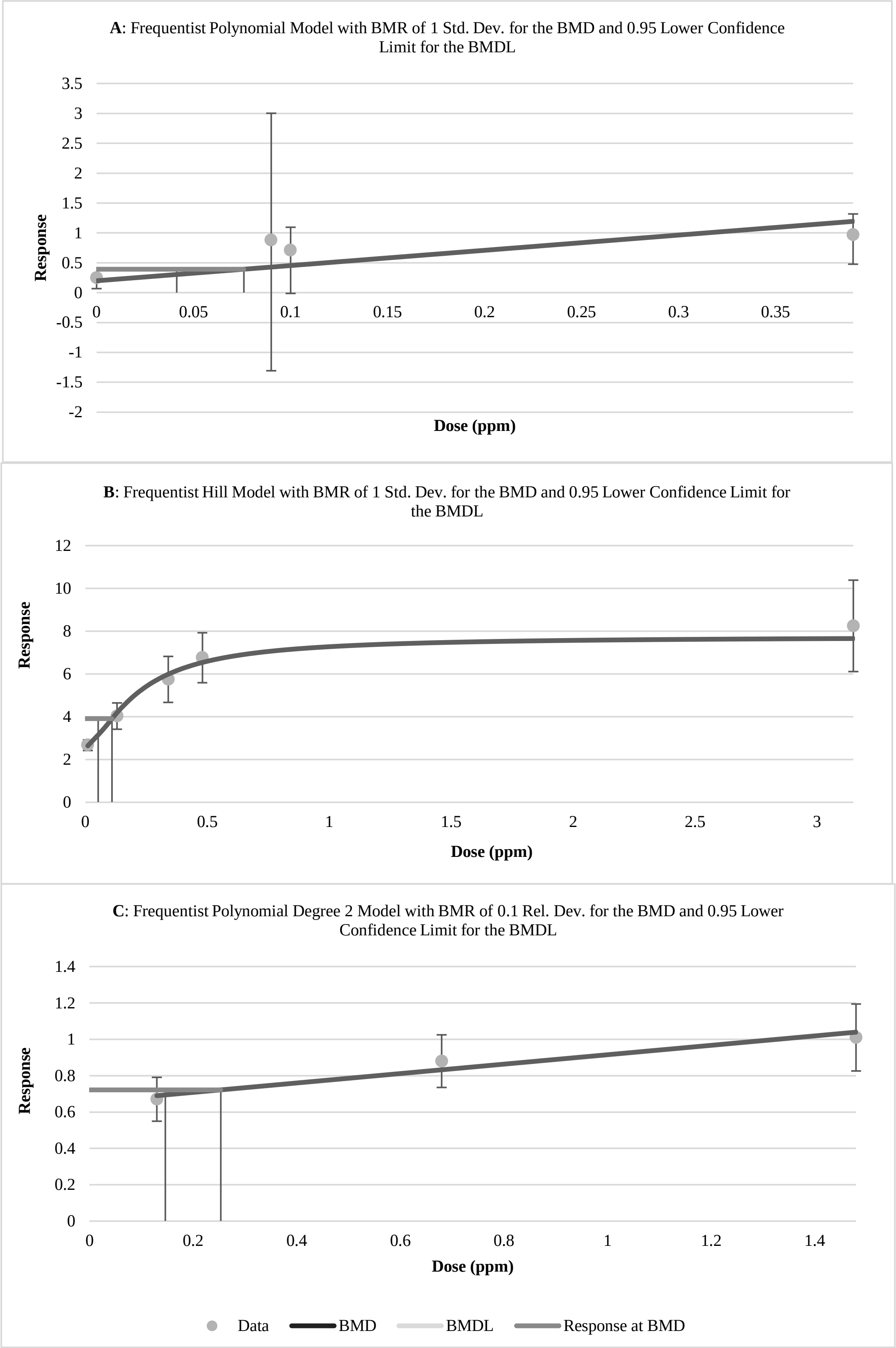

Figure 1. Dose-response curves for A: Ballrian's study based on micronucleus, B: Jiang's study based on micronucleus, and C: Lin's study based on comet assay

DISCUSSION

Irritation is a common effect of formaldehyde in inhalation exposure. American Conference of Governmental Industrial Hygienists (ACGIH) applies this effect to evaluate the occupational exposure threshold limit value [26]. The suggested standard in international society can estimate the risk of irritant effect. On the other hand, the incidence of carcinogenic effects produced by formaldehyde exposure was repeatedly shown in epidemiological studies [10]. The occurrence of carcinogenetic properties was predicted by different biological monitoring. In this study, BMD and BMDL of formaldehyde have been calculated according to the published paper for carcinogenetic risk assessment. BMDL, the lower confidence limit of the benchmark dose, is considered a better judgment for humans risk assessment [27].

In this study, BMD 0.062 and BMDL 0.03 ppm were determined for micronuclei damage in nasal mucosa cells of the formaldehyde-exposed workers[23]. Male and female workers were all non-smokers. No dose-response relationship was noted [23]. Nonetheless, this correlation could be observed via the accepted models in BMD software.

BMD 0.09 and BMDL 0.04 ppm were estimated based on micronuclei damage in peripheral blood lymphocytes of males and females exposed to formaldehyde. A dose-response relationship was observed between the five subgroups [24]. BMD and BMDL values in this study are higher than those [23]. One reason can be the difference in the contact site. Nasal mucosa cells are directly exposed to formaldehyde so that DNA damage can occur at lower concentrations. the highest BMD and BMDL for DNA strand breaks was obtained in peripheral blood lymphocytes [25]. As is clear, the BMDL is higher here than that of nasal mucosa cells.

a BMD 0.054 and BMDL 0.034 ppm were calculated for the occurrence of micronucleus in peripheral blood lymphocytes of workers exposed to formaldehyde [22]. In our previous study, the BMD 0.08 and BMDL 0.028 ppm were determined using the comet assay parameters in melamine workers for the genotoxic effects of formaldehyde [21]. Although the contact site is different, these BMDL are consistent with that of Ballarin's study.

This study evaluated the genotoxic effect on the 497 subjects in five studies by occupational exposure to formaldehyde. The BMDL level ranged from 0.028 to 0.04 ppm in four studies, that can be considered approximately equal. In the study [25] compared to others, BMDL has estimated about 5.4 times higher than, that excluded from results. Based on the results, the lowest BMDL related to a concentration of 0.028 ppm was selected for the genotoxicity risk evaluation.

The World Health Organization (WHO) has accepted a limit of 0.08 ppm of formaldehyde to prevent nasal and other cancers [28]. It was presented that nasopharyngeal cancer in humans has not been observed by formaldehyde exposure below 1.02 ppm [9]. Moreover, a NOAEL value of 2 ppm was confirmed for respiratory tract carcinogenicity in animal studies [28]. All of the estimated BMDL in our study was lower than these suggested levels. The National Institute of Safety and Health (NIOSH) proposed a standard for the carcinogenicity of formaldehyde. They considered a time-weighted average of 0.03 ppm for occupational exposure formaldehyde. The Asian population has the most role for BMDL estimation in our study. It seems that the genotoxic effect in Asian subjects has been acknowledged at the concentration upper than 0.03 ppm. However, recommended by NIOSH, the threshold limit value of formaldehyde is appropriate measure for carcinogenetic risk assessment. This endpoint can be considered as an appropriate measure and safe limits for cancer and genotoxic damages in the human studies.

CONCLUSIONS

Risk assessment of chemicals is a crucial step to adopting prevention strategies. This study investigated formaldehyde genotoxic risk according to the BMDL assessment. BMDL of formaldehyde was evaluated based on the published papers in an occupational setting. The lowest level of BMDL (0.028 ppm) was considered the basic value for assessing genotoxicity risk. According to our results, the time-weighted average of NIOSH is suggested to evaluate formaldehyde carcinogenic properties. However, formaldehyde, in a concentration higher than 0.03 ppm, has the risk of a genotoxic effect. One of the limitations of our study was the limited number of studies performed in occupational environments having appropriate dose-response data, and there is a need for re-evaluation of suggested BMDL in the future.

ACKNOWLEDGEMENTS

We appreciate the authors of all published papers in this context that provide data to estimate the BMDL for genotoxic risk assessment of formaldehyde**.**

Conflict of interest

The authors declare no conflict of interest

Compliance with ethical guidelines

This research does not contain any studies with human participants or animals performed by any of the authors

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

REFERENCES

1. Zhang Z.F., Zhang X., Zhang X.M., Liu L.Y., Li Y. F., Sun W., 2020. Indoor occurrence and health risk of formaldehyde, toluene, xylene and total volatile organic compounds derived from an extensive monitoring campaign in Harbin, a megacity of China. Chemosphere. 250, 126324.
2. Bolt H., Johnson G., Nielsen G., Papameletiou D., Klein C., 2016. SCOEL/REC/125 Formaldehyde Recommendation from the Scientific Committee on Occupational Exposure Limits. Scientific Committee on Occupational Exposure Limits
3. Yalcin E., Cavusoglu K., Cicek F., Demirtas G., Tasli B., 2015. Histopathological and Biochemical Changes in Swiss Albino Mice Induced by Formaldehyde: Protective Effect of Green Tea Extract. Cytologia. 80(4), 467-473.
4. Zendehdel R., Jouni F.J., Hajipour B., Panjali Z., Kheiri H., Vahabi M., 2017. DNA damage in workers exposed to formaldehyde at concentrations below occupational exposure limits. Toxicological & Environmental Chemistry. 99(9-10), 1409-1417.
5. Athanassiadis B., George G., Abbott P., Wash L., 2015. A review of the effects of formaldehyde release from endodontic materials. International Endodontic Journal. 48(9), 829-838.
6. Arts J.H., Rennen M.A., de Heer C., 2006. Inhaled formaldehyde: evaluation of sensory irritation in relation to carcinogenicity. Regulatory Toxicology and Pharmacology. 44(2), 144-160.
7. Nielsen G.D., Larsen S.T., Wolkoff P., 2013. Recent trend in risk assessment of formaldehyde exposures from indoor air. Archives of Toxicology. 87(1), 73-98.
8. IARC, 2012. Chemical Agents and Related Occupations. IARC Monogr Eval Carcinog Risks Hum 100F.
9. WHO, 2010. WHO guidelines for indoor air quality: selected pollutants.
10. US-EPA, 2010. Toxicological Review of Formaldehyde -Inhalation Assessment, http://cfpub.epa.gov/ncea/cfm/.
11. Bernardini L., Barbosa E., Charão M. F., Brucker N., 2020. Formaldehyde toxicity reports from *in vitro* and *in vivo* studies: a review and updated data. Drug Chem Toxicol. 1-13.
12. Ye X., Ji Z., Wei C., McHale C.M., Ding S., Thomas R., Yang X., Zhang L., 2013. Inhaled formaldehyde induces DNA–protein crosslinks and oxidative stress in bone marrow and other distant organs of exposed mice. Environ Mol Mutagen. 54(9), 705-718.
13. Ladeira C., Viegas S., Carolino E., Prista J., Gomes M. C., Brito M., 2011. Genotoxicity biomarkers in occupational exposure to formaldehyde—the case of histopathology laboratories. Mutation Research/Genetic Toxicology and Environmental Mutagenesis. 721(1), 15-20.
14. Albertini R.J., Kaden D.A., 2017. Do chromosome changes in blood cells implicate formaldehyde as a leukemogen? Crit Rev Toxicol. 47(2), 145-184.
15. Öberg M., 2010. Benchmark dose approaches in chemical health risk assessment in relation to number

and distress of laboratory animals. Regulatory Toxicology and Pharmacology. 58(3), 451-454.

16. Davis J.A., Gift J.S., Zhao Q.J., 2011. Introduction to benchmark dose methods and US EPA's benchmark dose software (BMDS) version 2.1. 1. Toxicology and Applied Pharmacology. 254(2), 181-191.

17. Weldon B.A., Griffith W.C., Workman T., Scoville D.K., Kavanagh T.J., Faustman E.M., 2018. *In vitro* to *in vivo* benchmark dose comparisons to inform risk assessment of quantum dot nanomaterials. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 10(4), e1507.

18. WHO, 2009. World Health Organization: Principles for modelling dose-response for the risk assessment of chemicals.

19. ECHA, 2012. Guidance on information requirements and chemical safety assessment. Chapter R. 8: Characterisation of dose [concentration]-response for human health. Chapter R, 8

20. Kamata E., Nakadate M., Uchida O., Ogawa Y., Suzuki S., Kaneko T., Ssito M., Kurokawa Y., 1997. Results of a 28-month chronic inhalation toxicity study of formaldehyde in male Fisher-344 rats. The Journal of Toxicological Sciences. 22(3), 239-254.

21. Zendehdel R., Vahabi M., Sedghi R., 2018. Estimation of formaldehyde occupational exposure limit based on genetic damage in some Iranian exposed workers using benchmark dose method. Environmental Science and Pollution Research. 25(31), 31183-31189.

22. Wang K., Wang T., Xu J., Zhu Y., Jian L., Au W., Xia Z., 2019. Determination of benchmark dose based on adduct and micronucleus formations in formaldehyde-exposed workers. International Journal of Hygiene and Environmental Health. 222(5), 738-743.

23. Ballarin C., Sarto F., Giacomelli L., Bartolucci G.B., Clonfero E., 1992. Micronucleated cells in nasal mucosa of formaldehyde-exposed workers. Mutation Research/Genetic Toxicology. 280(1), 1-7.

24. Jiang S., Yu L., Cheng J., Leng S., Dai Y., Zhang Y., Niu Y., Yan H., Qu W., Zhang C., 2010. Genomic damages in peripheral blood lymphocytes and association with polymorphisms of three glutathione S-transferases in workers exposed to formaldehyde. Mutation Research/Genetic Toxicology and Environmental Mutagenesis. 695(1), 9-15.

25. Lin D., Guo Y., Yi J., Kuang D., Li X., Deng H., Huang K., Guan L., He Y., Zhang X., 2013. Occupational exposure to formaldehyde and genetic damage in the peripheral blood lymphocytes of plywood workers. Journal of Occupational Health. 55(4), 284-291.

26. ACGIH, 2020. Threshold limit values for chemical substances and physical agents and biological exposure indices, http://www.acgih.org/tlv-bei-guidelines/.

27. USEPA, 2012. Benchmark Dose Technical Guidance. Risk Assessment Forum. Washington, DC 20460. EPA/100/R-12/001. . US Environmental Protection Agency

28. Nielsen G.D., Larsen S.T., Wolkoff P., 2017. Re-evaluation of the WHO (2010) formaldehyde indoor air quality guideline for cancer risk assessment. Archives of Toxicology. 91(1), 35-61.